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Associations between long-term exposure to air pollution, glycosylated hemoglobin, fasting blood glucose and diabetes mellitus in northern France

Margaux Riant[a], Aline Meirhaeghe[b], Jonathan Giovannelli[c], Florent Occelli[d], Anais Havet[a,d], Damien Cuny[d], Philippe Amouyel[c], Luc Dauchet[c,*]

[a] *CHU Lille, Epidemiology, Health Economics and Prevention Service, F-59000 Lille, France*
[b] *Inserm UMR1167 - RID-AGE Risk Factors and Molecular Determinants of Aging-related Diseases, Institut Pasteur de Lille, Université de Lille, Lille, France*
[c] *Inserm UMR1167, RID-AGE, Risk Factors and Molecular Determinants of Aging-Related Diseases, Université de Lille, Centre Hosp. Univ Lille, Institut Pasteur de Lille, Lille, France*
[c] *Univ. Lille, EA4483 - IMPECS (IMPact of Environmental ChemicalS on Human Health), F-59000 Lille, France*

A R T I C L E I N F O

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A B S T R A C T

Introduction: A growing body of evidence suggests that long-term exposure to air pollutants like nitrogen oxides (NO_x) and particulate matter (PM) is associated with the prevalence and incidence of type 2 diabetes mellitus. Serum glucose and glycosylated hemoglobin (HbA1c) levels are biomarkers of glucose homeostasis. Data on the association between glucose homeostasis biomarkers and air pollution are scarce. HbA1c and fasting blood glucose (FBG) concentrations have been linked to PM and NO_2 exposure in Taiwan, where mean pollution levels are 3 to 7 times higher than the guideline maximum annual mean values of 40 $\mu g/m^3$ (for NO_2) and 20 $\mu g/m^3$ (for PM10) set by the World Health Organization (WHO). However, this association is not consistently reported at lower levels of pollution. The objective of the present study was to investigate the relationships between long-term exposure to air pollution at the place of residence, diabetes biomarkers, and prevalent diabetes in two cities with relatively low level of pollution.

Methods: Data were recorded for 2895 adults (aged 40 to 65) having participated in the 2011–2013 ELISABET cross-sectional survey of the Lille and Dunkirk urban areas in northern France. Using multiple logistic and generalized linear regression models, we analyzed the associations between individual exposure to pollution on one hand and HbA1c, FBG and prevalent diabetes mellitus (DM) on the other. An atmospheric dispersion modelling system was used to assess annual exposure at the place of residence to coarse particulate matter (PM10), NO_2, and sulfur dioxide (SO_2).

Results: The median pollutant levels were 21.96 $\mu g/m^3$ for NO_2, 26.75 $\mu g/m^3$ for PM10, and 3.07 $\mu g/m^3$ for SO_2. A 2 $\mu g/m^3$ increment in PM10 was associated with an HbA1c increment [95% confidence interval] of 0.044% [0.021; 0.067]. This association was still statistically significant after adjustment for the neighborhood's characteristics. A 5 $\mu g/m^3$ increment in NO_2 was associated with an HbA1c increment of 0.031% [0.010; 0.053]. Associations between DM or FBG and air pollution did not achieve statistical significance.

Conclusion: Our study of a middle-aged, urban population evidenced an association between elevated HbA1c levels and long-term exposure to PM10 and NO_2 pollution levels that were relatively low but close to the WHO's guideline maximum values.

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; EDI, European deprivation index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INSEE, French National Institute for Statistics and Economic Studies; IRIS, regrouped statistical information block; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OR, odds ratio; PM, particulate matter; PM2.5, fine (< 2.5 μm) particulate matter; PM10, coarse (≤ 10 μm) particulate matter; SO_2, sulfur dioxide; T2DM, type 2 diabetes mellitus; WHO, World Health Organization

* Corresponding author at: Service d'Épidémiologie, Économie de la Santé et Prévention, Maison Régionale de la Recherche Clinique, CHRU de Lille, 2 rue du Pr Laguesse, F-59037 Lille Cedex, France.
E-mail address: luc.dauchet@chru-lille.fr (L. Dauchet).

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1. Introduction

1.1. Context

Type 2 diabetes mellitus (T2DM) is the 11th leading cause of years of life lost, whereas ambient air pollution is the 7th leading risk factor for the global burden of disease in countries with a high socio-demographic index (GBD 2016 Causes of Death Collaborators, 2017; GBD 2016 Risk Factors Collaborators, 2017). A growing body of evidence suggests that long-term exposure to air pollutants (such as nitrogen oxides (NO_x) and particulate matter (PM)) is associated with the prevalence and incidence of T2DM (Andersen et al., 2012; Coogan et al., 2016; Eze et al., 2014; Honda et al., 2017; Krämer et al., 2010; Liu et al., 2016; Park et al., 2015; Renzi et al., 2018; Weinmayr et al., 2015). However, a number of other studies have failed to find significant associations (Brook et al., 2008; Dijkema et al., 2011; Puett et al., 2011).

Serum glucose and glycosylated hemoglobin (HbA1c) levels are biomarkers of glucose homeostasis. Whereas serum glucose values can vary markedly over a short period of time, HbA1c is an accepted marker of an individual's mean blood glucose level over the previous 30 to 120 days (Saudek et al., 2006). Therefore, HbA1c might be a better indicator in studies of a putative association between diabetes mellitus (DM) and long-term exposure to air pollution. The risk of complications in diabetic patients increases as HbA1c rises (Zoungas et al., 2012). Furthermore, elevated HbA1c is reportedly linked to total mortality in the general population (Cohen et al., 2009).

Data on the association between glucose homeostasis biomarkers and air pollution are scarce. In newly diagnosed patients with T2DM in Germany, higher PM10 levels (reported on the regional level) were associated with higher HbA1c concentrations (Tamayo et al., 2014). HbA1c and fasting blood glucose (FBG) concentrations have been linked to PM and NO_2 exposure in Taiwan (Chuang et al., 2011) and in China (Liu et al., 2016), where mean pollution levels are 3 to 7 times higher than the maximum guideline annual mean values of 40 μg/m^3 (for NO_2) and 20 μg/m^3 (for PM10) set by the World Health Organization (WHO) (World Health Organization. Occupational and Environmental Health Team, 2006). At lower levels of pollution, however, this association is not consistently observed; a nationwide study in the USA found a significant association between air pollution and HbA1c (Honda et al., 2017), whereas a study of a city and two rural areas in southern Germany did not (Wolf et al., 2016).

The objective of the present study (performed in the Lille and Dunkirk urban areas of northern France) was to investigate the association between residential exposure to atmospheric NO_2, PM10 and SO_2 on one hand, and levels of HbA1c, fasting blood glucose, and DM (types 1 and 2 pooled) on the other. Levels of air pollution in the Lille and Dunkirk urban areas are relatively low but are close to the WHO's maximum guideline values.

2. Methods

2.1. Study population

Our analysis was based on the cross-sectional Enquête Littoral Souffle Air Biologie Environnement (ELISABET) survey. The latter included a representative sample of men and women (aged from 40 to 65) in the Lille and Dunkirk urban areas. Both areas have high traffic levels, and Dunkirk has a large industrial area. All participants were recruited between January 2011 and November 2013. The ELISABET study's methodology has been described in detail elsewhere (Clement et al., 2017; Giovannelli et al., 2017; Hulo et al., 2016; Quach et al., 2015). Most of the data were collected at home; a trained, registered nurse administered a detailed questionnaire and collected a blood sample and anthropomorphic data. The study protocol was approved by the local investigational review board (*CPP Nord Ouest IV*, Lille, France; reference: 2010-A00065-34; ClinicalTrials.gov identifier: NCT02490553), in compliance with the French legislation on biomedical research. All participants provided their written, informed consent to participation in the study.

In the present analysis, we selected participants who had lived at their current address for at least one year. Participants with missing data for age, sex, body mass index (BMI), educational level, smoking status and physical activity and those with a non-localizable place of residence were excluded. For each outcome (prevalent DM, HbA1c, and FBG), we selected participants who had a full dataset for assessment. Participants taking diabetes medication were excluded from our analysis of the association between air pollution and HbA1c and FBG. Lastly, participants who had not being fasting for more than 10 h at the time when the blood sample was collected (in the ELISABET study's case report form, the duration of fasting was reported as more than 10 h or < 10 h; the exact duration of fasting was not documented) were excluded from our analysis of the association between pollution and FBG.

2.2. Pollution data

Between 2010 and 2013 in Lille and between 2012 and 2013 in Dunkirk, the annual mean concentrations of SO_2 (in Dunkirk only), NO_2 and PM10 were estimated by the *ATMO – Nord Pas de Calais* monitoring organization, using an atmospheric dispersion modelling system. The latter incorporated meteorological, topographic and land-use data, pollutant emissions from natural sources or related to human activity, and ambient air pollution data from monitoring stations. Concentration maps for NO_2 and PM10 in Lille and Dunkirk in 2015 are shown on the ATMO website (ATMO Nord-Pas-de-Calais, 2016a, 2016b). We used a spatial resolution of 25 × 25 m. Each participant's place of residence was located within this 25 m grid. We assessed the annual exposure levels at the place of residence as the mean value of the four closest points in the grid, weighted by the inverse square distance to each point (Babak and Deutsch, 2009). The overall pollution exposure for each participant was then calculated as the average level of pollution over the year of their inclusion and the years before. For participants included in 2011 in Dunkirk, we used the 2012 pollution levels as the measure of exposure because the pollutant concentrations in 2011 were not available.

2.3. Neighborhood data

The median income and population density for each neighborhood were extracted from data provided by the French National Institute for Statistics and Economic Studies (INSEE). We also used data from the INSEE to calculate the European deprivation index (EDI) (Pornet et al., 2012) for each neighborhood. The geographical unit for a neighborhood corresponded to the French "regrouped statistical information block" (IRIS) unit, as defined by the INSEE. The IRIS unit is the smallest census unit available in France.

2.4. Outcome assessment

Diabetes mellitus was defined as ongoing treatment with insulin or oral antidiabetic medication, a HbA1c level ≥6.5%, a fasting blood glucose level ≥1.26 g/L or a non-fasting blood glucose level ≥2 g/L (Weinmayr et al., 2015). We could not differentiate between types 1 and 2 DM.

The HbA1c level in a sample of whole blood was measured using high-performance liquid chromatography (VARIANT II, Bio-Rad). The glucose level in a sample of fluorinated plasma was measured using a spectrophotometric hexokinase enzyme assay (AU480, Beckman Coulter). From January to March 2011, blood assays were performed in the central laboratories at the Pasteur Institute of Lille and at Lille University Medical Center. From April 2011 to November 2013, all